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Case report

Hemolytic anemia due to hydrochlorothiazide: A case report

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ABSTRACT

Drug-associated hemolytic anemia is very rare. Hydrochlorothiazides are commonly used as diuretic or antihypertensive agents. In this report, we present an 80-year-old male patient who developed hemolytic anemia 20 days after using a combination of angiotensin receptor blocker and hydrochlorothiazide for the treatment of hypertension.

Introduction

Autoimmune hemolytic anemia due to drugs is an immunologic condition characterized by the destruction of red blood cells induced by the antibodies that bind to the surface antigens of red blood cell membranes.[1] Hydrochlorothiazides are commonly used diuretic or antihypertensive agents. While immune hemolytic anemia due to hydrochlorothiazide is rare, severe hemolytic anemia cases have been reported. In this study, we aimed to present a patient who had been taking hydrochlorothiazide for the treatment of hypertension and was thought to develop autoimmune hemolytic anemia due to the drug.

Case report

Eighty-year-old male patient admitted to the emergency unit for paleness, icterus of sclera, shortness of breath, weakness, fatigue, and chest pain that started 20 days ago and increased gradually. According to his medical history, he underwent aorto-coronary bypass surgery 15 years ago and had a stent implanted 3 years ago. ECG showed ST depression in derivations V1–V6. Troponin showed a normal level of 0.01 μg/L. The patient was diagnosed with acute coronary syndrome and taken to the coronary intensive care unit where anti-ischemic therapy was started. His hemoglobin (Hb) and hematocrit (Hct) values were 7.5 g/dL (normal range: 13.2–17.4 g/dL) and 21% (normal range: 39–51%), respectively. Of the erythrocyte indices, mean corpuscular volume (MCV) was 100 fL (normal range: 76–96 fL), mean corpuscular hemoglobin (MCH) was 23.6 pg/cells (normal range: 27–33 pg/cells), and mean corpuscular hemoglobin concentration (MCHC) was 27.1 g/dL (normal range: 30–35.5 g/dL). Fragmented normochromic red blood cells and anisocytosis were seen in the peripheral blood smear. Reticulocyte rate was found as 3%. In addition, thrombocyte count was 211×10^3/μL (normal range: $150–450 \times 10^3$/μL). Biochemical parameters were as follows: blood urea nitrogen 90 mg/dL (normal range: 10–50 mg/dL), serum creatinine 1.1 mg/dL (normal range: 0.6–1.2 mg/dL), and serum sodium 136 mmol/L (normal range: 135–145 mmol/L) and potassium 4.8 mmol/L (normal range: 3.5–5.1 mmol/L). Of coagulation tests, prothrombin time (PT) was 13 s (normal range: 11–14 s), the reference range for international normalized ratio (INR) was 1.15 (normal range: 0.8–1.2), and activated partial thromboplastin time (aPTT) was 27.6 s (normal range: 21–36 s).

One unit of red blood cell suspension was given. Hb and Htc levels were increased to 9.6 g/dL and 24.6%, respectively; and then to 10.7 g/dl and 26.8%, respectively, following the administration of a second suspension of red blood cells. Vitamin B12 level was normal, folic acid level was low and ferritin level was high which were 242 pg/mL (normal range: 191–663 pg/mL), 4.5 ng/mL (normal range: 4.6–18.7 ng/mL) and 1080 ng/mL (normal range: 30–400 ng/mL), respectively. Control complete blood count values at day 2 were 8.5 g/dL for Hb and 22.1% for Hct. Consultation was requested from internal medicine department. Occult blood test in the stool was negative. Endoscopy was performed to exclude gastrointestinal bleeding. Thus, active gastrointestinal hemorrhage was excluded. Abdominal ultrasound revealed no intra-abdominal hematoma, mass, or hepatomegaly or splenomegaly. Indirect Coombs test was negative, but direct Coombs was positive as IgG + 2. Lactate dehydrogenase (LDH) was increased to 741 U/L (normal

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range: 240–480 U/L). Haptoglobin was <0.3 g/L (normal range: 0.3–2 g/L). Yes, total bilirubin and direct bilirubin levels were high which were 2.6 mg/dL (normal range: 0–1.2 mg/dL) and 1.1 mg/dL (normal range: 0–0.3 mg/dL), respectively. Urine analysis revealed proteinuria, and (+) bilirubin and (+++) hemoglobin. ANA serum dilution was negative. It was understood from his medical records that hemoglobin and Hct levels were 13.1 g/dL and 38.7%, respectively, 20 days ago. When his medical history was reviewed, it was seen that he was started on daily irbesartan 150 mg plus hydrochlorothiazide 12.5 mg for high blood pressure. The patient was then transferred to internal medicine clinic with the current findings for hemolytic anemia due to thiazide. Then, hydrochlorothiazide was stopped. After that, trandolapril was started for treatment of hypertension. The patient was put on follow-up program with periodic complete blood count analysis. At the end of the next following 2 weeks, a negative Coombs test result and a hemoglobin value of 10.5 g/dL were obtained. During follow-up, the hemoglobin values were 13.1 g/dL and 13.3 g/dL, 1 month later and 3 months later, respectively.

Discussion

Drug-associated hemolytic anemia is seen approximately in one out of a million individual. It may be lethal, possibly with no diagnosis established.[2] It was found out in 2007 that up to 125 different drugs may cause hemolysis.[3] Forty years ago, back when methyldopa and antibiotics like high doses of intravenous penicillin had been used commonly, most of the reported cases of hemolytic anemia were due to the use of these agents. Today, however, cases of hemolytic anemia are rather associated with cephalosporins since methyldopa is almost no more used and second- and third-generation cephalosporins are the leading antibiotics.[4,5]

Hemolytic anemia associated with drugs occurs through one of three basic mechanisms[6–9]: (i) drug absorption mechanism, where antibodies against the drug react with the adsorbed drug on the surface of red blood cell membrane. The antibody–antigen complex that is formed on the surface of red blood cell membrane is removed from the circulation by reticulo-endothelial system, thus resulting in extravascular hemolysis; (ii) immune complex mechanism, in which drug–antibody complex binds to the red blood cell membrane activating the complement cascade; this process leads to acute intravascular hemolysis; and (iii) auto-antibody type, in which antibodies against the drug bind to red blood cell membrane through cross reaction resulting in extravascular hemolysis (Table 2). (See Table 1.)

Anemia associated with hydrochlorothiazide is an example of immune complex-type immune hemolytic anemias. Intravascular hemolysis develops as a result of activation of complement system by the binding of the drug to the red blood cell membrane and may be severe and fatal. Anemia, fragmented red blood cells on peripheral smear, hyperbilirubinemia, increased levels of LDH, reticulocytosis, positive Coombs test, hemoglobinuria and findings related with organ failures may be observed depending on the severity of hemolysis.[5] In our case, an immune event was considered since anemia, weakness and shortness of breath were gradually increased after hydrochlorothiazide was started with the absence of an anemia 20 days ago, accompanied by the fall in hemoglobin values following the administration of red blood cell suspensions and a positive Coombs test. Presence of fragmented red blood cells, hyperbilirubinemia, hemoglobinuria and decreased levels of haptoglobin (<0.3, normal range over the age of 50: 0.47–2.1 g/L) were among findings that demonstrated an intravascular hemolysis in our case.

In practice, Coombs test is used to investigate and diagnose these types of hemolysis. This test is a laboratory method used to identify the presence of incomplete antibodies attached to the red blood cells or circulating freely and is also known as antiglobulin test.[10] Positive direct Coombs test may indicate a hemolysis that develops through an immune complex-type reaction. In our case, polyspecific direct Coombs test IgG was positive and indirect Coombs test was negative.

In 1976, Vila et al.[11] had observed, for the first time, the episodes in a 67-year-old patient whom they treated with a combination of methyldopa and hydrochlorothiazide for hypertension during 4 years and associated the mild to moderate hemolytic anemia with the thiazide fraction of the medication. In 1980, Garratty et al.[12] observed a severe immune hemolytic anemia and renal failure in a 24-year-old black patient who ingested 15–20 tablets of methyldopa plus hydrochlorothiazide to commit suicide. They associated the hemolytic anemia with the antibodies associated with hydrochlorothiazide through immune complex mechanism. In these two cases of intravascular hemolysis, antibodies were developed against hydrochlorothiazide but not against methyldopa. In 1986, Shirey et al.[13] considered hemolytic anemia due to a drug when direct antiglobulin tested positive in a 53-year-old black female. They found similar antibodies against diuretics by characterizing hydrochlorothiazide antibody in serologic studies and offered an alternate diuretic therapy for patients.

Mortality is reported to be 40% when hemolytic anemia associated with drugs is assessed where hemolytic anemia due to ceftriaxones is associated with higher mortality among them.[5] Beck et al.[14] observed a case of hemolytic anemia in a 53-year-old black male patient 18 months after starting hydrochlorothiazide and methyldopa. It was the first case that ended up with death after hemolytic anemia due to hydrochlorothiazide. The patient had a positive direct and indirect Coombs test, a low level of haptoglobin of 0.5 g/dL and a high LDH in whom cause of death could not be established in autopsy but was considered as fatal immune hemolytic anemia associated with the use of hydrochlorothiazide.

Anemia may sometimes immediately be demonstrated by serious clinical findings while the diagnosis may be delayed as long as

Table 1
Laboratory values of the patient.

Day	Hb (g/dL)	Hct %	RBCs 10^6/μL	Total bil. (mg/dL)	Direct bil. (mg/dL)	LDH (U/L)
20 d ago	3.1	38	4.00	0.35	0.35	294
Day 1	7.5	21	2.07	1.54	0.70	322
Day 2	9.6	26.8	2.41			
Day 3	10.7	26.8	2.69			255
Day 4	8.5	22.1	2.18	2.99	1.14	347
Day 5	9.5	24.2	2.40	2.46	741	
3 m later	13.3	40.5	3.87	0.55	0.21	382

Hb: hemoglobin; Htc: hematocrit; RBCs: red blood cells; Bil: bilirubin; LDH: lactate dehydrogenase; d: days; m: months.

Table 2
Mechanism of drugs that cause immune hemolytic anemia.

Mechanism	Drug absorption (Hapten)	Immune complex	Auto-antibody
DAT	Positive anti-IgG	Positive anti-C3	Positive anti-IgG
Location of hemolysis	Extravascular	Intravascular	Extravascular
Drug	Penicillin	Quinidine	Alpha-methyldopa
	Ampicillin	Phanecetin	Mefenamic acid
	Methicillin	Hydrochlorothiazide	L-Dopa
	Carbenicillin	Rifampin	Procainamide
	Cephalothin	Sulfonamide	Ibuprofen
	Cephalordin	Isoniazid	Diclofenac
		Insulin	Interferon Alpha
		Tetracycline	
		Melphalan	
		Acetaminophen	
		Hydralazine	
		Probenecid	
		Chlorpromazine	
		Streptomycin	
		Fluorouracil	
		Sulindac	

DAT: direct antiglobulin test.

1–2 weeks after the intake of the drug in cases without a serious hemolysis, and anemia may be associated with other causes without any established diagnosis.[15] In our patient, a moderate anemia accompanied by a mild increase in LDH levels and positive Coombs test were found 20 days after the intake of the drug since the hemolysis was not severe.

Cessation of the drug in mild cases and steroids plus supportive care in more severe cases are recommended.[16,17] In our patient, the moderate anemia was recovered without any treatment after stopping hydrochlorothiazide.

The diagnosis of hemolytic anemia associated with drugs was established in our patient based on medical history and clinical signs and symptoms. Presence of fragmented red blood cells and hemoglobinuria suggested an intravascular hemolysis.

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